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Association between deficient levels of vitamin D and the occurrence of selected retinal diseases

1. Aleksandra Żmijewska*

Railway Hospital of dr. Włodzimierz Roefler in Pruszków, Warsztatowa 1, 05-800 Pruszków, Poland, <https://orcid.org/0009-0002-6281-8943>,
zmijewskaleksandra@gmail.com

*corresponding author

2. Monika Maleszewska

Dr Anna Gostynska Wolski Hospital, Independent Public Health Care Institution, Marcina Kasprzaka 17, 01-211 Warsaw, Poland, <https://orcid.org/0009-0006-4623-7742>, monikamaleszewskaa@gmail.com

3. Mateusz Sztybór

Provincial Polyclinical Hospital in Płock of Marcina Kasprzaka, Medyczna 19, 09-400 Płock, Poland, <https://orcid.org/0009-0000-7511-3534>, mateuszszybor@onet.pl

4. Gabriela Nowak

County Health Center in Otwock Sp. z o.o., Batorego 44, 05-400 Otwock, Poland,
<https://orcid.org/0009-0000-4942-9914>, gabi098098098@gmail.com

5. Marcin Kapica

Health Care Team of the District Hospital In Sochaczew, Batalionów Chłopskich 3/7,
96-500 Sochaczew, Poland, <https://orcid.org/0009-0005-2191-034X>,
marcin_kapica@icloud.com

6. Julia Piątkiewicz

The Infant Jesus Teaching Hospital, Lindleya 4 02-005 Warszawa, Poland,
<https://orcid.org/0009-0005-1969-3593>, julia.piatkiewicz@onet.pl

7. Maria Krzyżanowska

Military Institute of Medicine - National Research Institute, Szaserów 128, 04-141
Warszawa, Poland, <https://orcid.org/0009-0002-2148-4414>,
mariaannakrzyzanowska@gmail.com

8. Karol Momot

Chair and Department of Experimental and Clinical Physiology, Laboratory of Centre
for Preclinical Research, Medical University of Warsaw, Banacha 1b, 02-097 Warsaw,
Poland, <https://orcid.org/0000-0001-8659-2948>, karolmomot@icloud.com

9. Mikołaj Wojtas

Health Care Team of the District Hospital In Sochaczew, Batalionów Chłopskich 3/7,
96-500 Sochaczew, Poland, <https://orcid.org/0009-0006-1092-3214>,
wojtas.m12@gmail.com

10. Karen Głogowska

The University Dental Center Medical University of Warsaw, Binieckiego 6, 02-097
Warsaw, Poland, <https://orcid.org/0009-0004-9869-3374>,
karen.glogowska@gmail.com

Abstract

Introduction and Purpose:

Vision originates in the eye's retina, a complex structure essential for processing visual information. The connection between nutritional inadequacy, particularly vitamin deficiencies, and overall health, including ocular health, has long been acknowledged. Recent studies highlight the potential impact of vitamin D, a crucial nutrient, on retinal health. The aim is to investigate the association between low levels of vitamin D and retinal diseases like age-related macular degeneration (AMD) and diabetic retinopathy (DR), and to evaluate the potential benefits of vitamin D supplementation or lifestyle changes for at-risk patients.

Description of the State of Knowledge:

AMD, a significant cause of blindness in the elderly, involves factors like oxidative stress and inflammation. Various stages of AMD require different treatments, with limited options for advanced stages. DR, a complication of diabetes, leads to conditions such as retinal ischemia and neovascularization. Both conditions are potentially influenced by vitamin D levels. Studies show mixed results regarding the impact of vitamin D on these diseases. Some suggest lower levels may increase risk, while others report no significant effect or even contradictory findings.

Conclusions:

While some studies indicate a potential association between low vitamin D levels and the occurrence of retinal diseases, discrepancies exist in the findings. Lower vitamin D concentrations may be linked to a higher frequency of AMD and DR, but the evidence is not consistent across all studies. Therefore, a more in-depth exploration of this subject is warranted to draw conclusive insights. It is crucial to consider supplementation or dietary changes in cases of vitamin D deficiency, given its potential impact on systemic health.

Keywords: vitamin D, age-related macular degeneration, diabetic retinopathy, retinal diseases

Introduction and purpose

Vision initiates in the eye's retina. The retina is categorized as part of the central nervous system (CNS) as it originates from the brain's diencephalon. It's a complex and multilayered structure, which plays a pivotal role in the detection, processing, and transmission of visual information to the brain. [1,2]

The connection between nutritional inadequacy and an individual's general health has long been recognized. Deficiencies in nutrition, encompassing both vitamins and minerals, have the potential to adversely impact the entire body, including the eyes. Commonly, vitamins are acquired and supplemented through dietary intake, as the body cannot produce some of them independently. [3, 32] Therefore, delving into the foundations of nutritional health can guide us toward more effective approaches in managing various retinal conditions. [3]

The latest studies have reported that vitamin supplementation may have an impact on the proper functioning of the retina. One of them is vitamin D, deficiency of which is a common phenomenon worldwide. It is said that vitamin D deficiency is defined as the level of 25-hydroxyvitamin less than 30 ng/ml. [41] It is a prohormone that dissolves in fat and is initially synthesized in the skin upon exposure to sunlight. [4] Unfortunately, with the exception of egg yolks or fatty fish (such as sardines, herring, tuna, mackerel, salmon), the natural presence of vitamin D in food is minimal unless it is fortified, as seen in milk, dairy products, orange juice, or margarines. [36,37,38]

Vitamin D is composed of a blend of vitamin D₂ (ergocalciferol), derived from animal sources, and D₃ (cholecalciferol), produced in plants and fungi. [32,38] Through various metabolic processes, it transforms into active vitamin D. The initial hydroxylation occurs in the liver, resulting in the synthesis of 25-hydroxyvitamin D (25(OH)D), also known as calcidiol. Following the second hydroxylation in the kidneys, calcidiol is converted into 1,25-dihydroxy vitamin D₃ (1,25(OH)₂D), alternatively referred to as calcitriol, overseeing the majority of biological functions. [4] Vitamin D is recognized for its role as a protective factor in various conditions, including cancer, cardiovascular and respiratory diseases, bone disorders, kidney issues, and other ailments. [5,19] Animal studies have demonstrated that vitamin D supplementation has the potential to diminish retinal inflammation. These findings indicate a potential role for vitamin D in preserving healthy retinal functions and safeguarding the retina against the aging process. [12]

The aim of the study is to investigate whether low levels of vitamin D in the body may be associated with the occurrence of retinal diseases such as age-related macular degeneration or diabetic retinopathy. Based on recent publications, it will be possible to determine whether supplementation or lifestyle changes are worthwhile for patients at risk of these diseases.

Materials and methods

A search was performed on the PubMed and Cochrane databases for literature published between 2018 and 2023, using specific keywords: "vitamin D", "retinal diseases", "age-related macular degeneration ", "vitamin D AMD", "diabetic

retinopathy”, “vitamin D diabetic retinopathy”, “retinal cells”, “vitamin D supplementation”, “ocular diseases”.

Description of the state of knowledge

Age-Related Macular Degeneration

Age-related macular degeneration (AMD), a complex condition, poses significant threats to vision and stands as the one of leading causes of irreversible blindness among individuals aged 55 and older in developed nations, impacting millions of affected patients. [5] Noteworthy risk factors encompass smoking, nutritional elements, cardiovascular disorders and genetic markers. [11] However, the precise mechanisms behind AMD's development remain unclear. Recently, illness has been linked to various pathological factors, including oxidative stress and inflammation. [6,9] A defining trait of AMD is the buildup of extracellular deposits, primarily drusen, in the macula, the central region of the retina characterized by a high density of retinal photoreceptors, making it particularly sensitive to visual stimuli. [5,9]

AMD has been classified according to 3 clinical stages: early AMD, intermediate AMD and advanced AMD divided into atrophic (dry) or neovascular (wet or exudative) AMD. [5]

The neovascular form of age-related macular degeneration is typically treated with intravitreally injected inhibitors of vascular endothelial growth factor (VEGF). However, it requires frequent intravitreal injections and follow-up visits. [10] Currently, there is no treatment to halt the vision loss associated with the increasing dry form of AMD. Consequently, research on dry AMD therapy is expanding, investigating options like steroids, antioxidants, and neuroprotective agents tested in vitro and in vivo to slow down the disease progression. [13]

Antonio Pérez Serena et al., wanted to ascertain whether the level of vitamin D in the body has an impact on the occurrence of age-related macular degeneration in patients. Participants were classified into four AMD groups (early, intermediate, advanced atrophic, and advanced neovascular) and those without any macular degeneration - free control group. Exclusions were made for individuals with specific

medical conditions and those taking vitamin D supplements. In the group of 93 AMD patients, as many as 89.2% suffered from vitamin D deficiency (<30 ng/ml), while in the research group (also 93 patients), this figure was 79.6%. The severe deficiency (<10 ng/ml) and deficiency (10-19 ng/ml) of vitamin D was also higher among AMD patients compared to the control group - 16.1% and 50.5% for AMD patients, 11.8% and 31.2% for the control group, respectively. Nevertheless, the median levels of vitamin D in early AMD, intermediate AMD, advanced dry AMD, and advanced neovascular AMD were not statistically significant. This study indicates that individuals with AMD exhibited reduced vitamin D levels in comparison to those without the condition. [5]

Emrah Kan et al., investigated the association between vitamin D levels and exudative age-related macular degeneration. They concluded that patients with vitamin D deficiency more frequently exhibit exudative age-related macular degeneration. A vitamin D deficiency below 20 ng/ml was observed in 81.1% of patients with wet AMD (95 patients), compared to 66.3% in the control group (also 95 patients). However, the percentage of patients in the control group with a normal vitamin D level (above 30 ng/ml) was similar compared to the group of patients with neovascular AMD, with figures of 9.5% and 7.4%, respectively. [6]

In an article published in 2019 by Amy E. Millen et al., the aim of the study was to establish the association between vitamin D concentrations at visit 2 (1990–1992) and the 18-year incidence of AMD spanning from visit 3 (1993–1995) to visit 5 (2011–2013). During the visit 2, the patients' vitamin D levels were collected. Retinal fundus photographs were taken during the visit 3 and 5. The authors assessed the occurrence of any, early, and late stages of AMD. In the end, an analytic sample of 1225 participants took part in the study. This research suggests that higher concentrations of vitamin D (> 70 nM), might be linked to a reduced likelihood of developing early AMD. However, no statistically significant findings were noted regarding pigmentary abnormalities or the occurrence of incident late AMD. [8]

In another study conducted on the Turkish population by Naciye Kabataş et al., focusing on the influence of vitamin D on AMD, 216 patients participated, including

102 belonging to the control group. Patients were divided into three groups based on the advancement of the disease. The average levels of serum vitamin D in the study group were 14.4 ± 9.6 ng/ml, while in the control group, it was 29.4 ± 14.6 ng/ml. The levels of vitamin D were discovered to be notably lower in advanced-stage AMD (10.9 ± 6.8 ng/ml) compared to early- and intermediate-stage AMD. However, there was no significant difference observed between patients with early- and intermediate-stage AMD. It appears that in patients with AMD, the concentration of vitamin D was lower. [12]

William G. Christen et al., wanted to assess whether the daily supplementation of vitamin D3, marine ω -3 fatty acids, or a combination of both could prevent the onset or advancement of AMD. The participants in the research group were receiving 2000 IU of Vitamin D3 daily, along with/or a daily intake of 1g of marine ω -3 fatty acids. A total of 25871 individuals were included in the study. The study had predefined endpoints. The main endpoint was the occurrence of total AMD events, which encompassed both newly diagnosed AMD cases and cases where AMD progressed to an advanced stage among participants who already had AMD at the beginning. Secondary endpoints included the specific components contributing to the primary endpoint, newly diagnosed cases of visually significant AMD (20/30 or worse) among individuals without AMD initially, and newly diagnosed cases of advanced AMD, encompassing neovascular AMD and central geographic atrophy, among those without AMD at the study's outset. Out of the participants randomly selected, 15787 individuals submitted an initial blood sample eligible for 25-hydroxyvitamin D analysis. Within this group, the average serum total 25-hydroxyvitamin D level measured 30.8 ng/ml. In a subset of 1644 participants subjected to recurring measurements after one year, the mean 25-hydroxyvitamin D levels elevated from 29.8 ng/ml at the baseline to 41.8 ng/ml after 1 year in the vitamin D3 group, while showing minimal changes in the placebo group. During a median follow-up period of 5.3 years of treatment, a confirmed AMD event was observed in 324 participants. In the treated group, there were 163 cases, while in the placebo group, there were 161 cases. This event included 285 cases of newly diagnosed AMD and 39 instances of AMD progression. Upon examination of predefined secondary endpoints, there were no

noteworthy distinctions noted between the groups concerning visually significant AMD, with 134 occurrences, or incident advanced AMD, with 93 events. This indicates that the results are similar, and there is no significant association between vitamin D supplementation and AMD. [7]

Diabetic Retinopathy

Diabetic retinopathy (DR) stands out as the prevalent and distinctive microvascular complication associated with diabetes, leading to conditions such as retinal ischemia, neovascularization, altered retinal permeability and macular edema. [39] It ranks among the foremost contributors to vision impairment in individuals aged 50 and above. The progression of diabetic retinopathy initiates with non-proliferative diabetic retinopathy (NPDR) and progresses to an advanced stage known as proliferative diabetic retinopathy (PDR). [14,15] The primary treatment for DR currently involves intravitreal injections of anti-VEGF and steroid agents, laser treatments, vitreoretinal surgery and of course glucose control. [16,39] Various risk factors are linked to retinopathy in individuals with diabetes, with age, duration of diabetes, high body mass index, hyperglycemia, high blood pressure and hypercholesterolemia being the most significant factors. [40] According to some articles, there is a potential connection between diabetic retinopathy and inflammation, as well as the dysregulation of various inflammatory mediators. [17]

Wei-Jing Zhao et al., examined how vitamin D levels affect microvascular complications (diabetic retinopathy, diabetic nephropathy, diabetic peripheral neuropathy) in individuals with type 2 diabetes mellitus. 815 patients participated in the study. The control group included 314 patients, the group with diabetic retinopathy comprised 235 patients, and the remaining individuals had other microvascular complications. The average vitamin D concentration in the DR group was 16.38 ± 9.16 ng/ml, while in the control group, it was 16.23 ± 7.10 ng/ml. Therefore, the study's conclusion was that vitamin D levels do not have an impact on the occurrence of diabetic retinopathy. [18]

The study, authored by Mehrdad Afarid et al., examined the influence of vitamin D concentration on the occurrence of diabetic retinopathy. The research involved 30

patients diagnosed with diabetic retinopathy and 30 patients without retinopathy. Among patients diagnosed with DR, 21 individuals displayed non-proliferative diabetic retinopathy, and 9 patients manifested proliferative diabetic retinopathy. In individuals with diabetic retinopathy, all patients displayed mild vitamin D deficiency, with levels ranging from 10 to 20 ng/ml. The average serum vitamin D concentration in patients with DR was lower compared to those without DR. [21]

Gauhar Nadri et al. investigated the association between vitamin D concentration and the occurrence of proliferative diabetic retinopathy. 72 consecutive individuals diagnosed with type 2 diabetes mellitus were enrolled in the study. The study population consisted of four groups: diabetes mellitus without retinopathy (24 patients), non-proliferative diabetic retinopathy (24 patients), proliferative diabetic retinopathy (24 patients), and healthy controls (24 patients). In the control group, the vitamin D concentration was 25.9 ± 1.60 ng/ml, in patients without DR it was 23.30 ± 2.01 ng/ml, in patients with NPDR it was 18.10 ± 1.90 ng/ml, and in patients with PDR it was 14.10 ± 1.20 ng/ml. The study's findings suggest that a serum vitamin D level equal to or less than 18.6 ng/ml can indicate the presence of proliferative disease in patients with diabetic retinopathy. Additionally, we can infer that lower concentrations of vitamin D are associated with a higher frequency of DR occurrence. [26]

Elise Girard et al. conducted a study on a group of 600 patients with diabetes, but only 361 had their vitamin D concentration measured during the first visit, at a hospital in French Guinea. Among 239 patients, the vitamin D level was less than 30 ng/ml (66.48%), and 97 of them had a vitamin D deficiency, with levels below 20 ng/ml. A total of 41 patients had DR, with 22 having normal vitamin D levels and 19 experiencing vitamin D deficiency. Nevertheless, individuals with diabetic retinopathy exhibited significantly higher median vitamin D concentrations compared to those without retinopathy, with levels of 31 ng/ml versus 26 ng/ml, respectively. [22]

Conclusions

It is challenging to provide a definitive answer regarding the impact of vitamin D levels on retinal diseases due to variations in the findings presented in the referenced

studies. Above, several examples were cited regarding the impact of vitamin D levels on the occurrence of age-related macular degeneration. In the most literature reviews, it can be observed that some authors of publications are of the opinion that low vitamin D levels may influence the frequency of disease occurrence. [5, 6, 8, 12, 25, 35] However, a different study found that a higher concentration of vitamin D in the serum was linked to an increased likelihood of early AMD and a decreased likelihood of late AMD [24], while according to another article, a high level of vitamin D was associated with a lower likelihood of developing early AMD. [8] In different study, researchers concluded that the concentration level of vitamin D has no influence on the occurrence of AMD. [7]

In the case of the influence of vitamin D concentration on the occurrence of diabetic retinopathy, the results of the cited studies were also varied. The majority of the cited publications conclusions suggest that low vitamin D concentrations are related to the occurrence of diabetic retinopathy. [20, 21, 23, 26, 27, 28, 29, 30, 31, 33, 34] In several of them, there was also mention of an elevated risk of developing proliferative diabetic retinopathy. [26, 27, 31, 33, 34] However, according to a study conducted by Elise Girard et al., patients with DR had a higher median vitamin D concentration compared to those without DR. [22] In yet other studies, the results indicate that vitamin D concentration does not have an impact on the occurrence of the disease. [18]

Despite discrepancies in some of the cited studies, we can conclude that lower vitamin D concentrations are likely associated with a more frequent occurrence of the mentioned retinal diseases. Nevertheless, given the inconclusive outcomes of the studies, a more in-depth exploration of this subject is necessary.

However, it is worth remembering that in the case of a deficiency in this vitamin, supplementation or consuming food rich in it, should be considered, because low concentrations may lead to the occurrence of various systemic diseases. [5,19]

Disclosures

Author's contribution

Conceptualization: Aleksandra Żmijewska, Monika Maleszewska; Methodology: Karol Momot, Mikołaj Wojtas; Formal analysis: Julia Piątkiewicz, Marcin Kapica; Investigation: Maria Krzyżanowska, Karen Głogowska; Writing - rough preparation: Gabriela Nowak, Mateusz Sztybór; Writing - review and editing: Aleksandra Żmijewska, Monika Maleszewska; Supervision: Aleksandra Żmijewska, Monika Maleszewska.

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